CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020766

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-766

MAY 12 1998

Hoffmann-La Roche Inc.
Attention: Ms. Peggy Jack
Program Director
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

Please refer to your new drug application dated November 26, 1996, withdrawn August 27, 1997, resubmitted November 14, 1997, received November 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (orlistat) Capsules, 120 mg.

We acknowledge receipt of your submissions dated January 15, 22, 28(5), 29(3), and 31, February 3, 4(2), 5(2), 10(2), 11(2), and 24, March 4, 5, and 24, April 9(2), 28, and 29, May 12 and 23, June 3(2), 10, 13, and 16, July 15, 23, 24, and 30, August 15, 21(2), and 27(3), and September 4, 25, and 30, 1997; and January 30, February 4(2), 5, 6, 18(3), and 20(2), March 3(2) and 5, April 1, 9, and 21, and May 9, 1998. The goal date for this application is May 17, 1998.

We have completed the review of this application as submitted with draft labeling. At this time, the application is approvable; however, final approval is contingent upon submission and review of additional data that support a conclusion orlistat does not increase the risk of breast cancer. These data should come from randomized, double-blind, placebo-controlled, parallel-group clinical studies. In the aggregate, these data should provide information on approximately as many women 45 years of age or older, and approximately as many women-years of treatment with orlistat 120 mg t.i.d. and with placebo, as did the clinical studies that showed an increase in the occurrence of breast cancer in women 45 years of age or older who were treated with orlistat 120 mg t.i.d. compared to the occurrence in otherwise similar women who were treated with placebo. In addition, changes to the labeling will be required after the additional data have been received.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Maureen Hess, MPH, RD, Consumer Safety Officer at (301) 827-6411.

Sincerely yours,

/S/

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

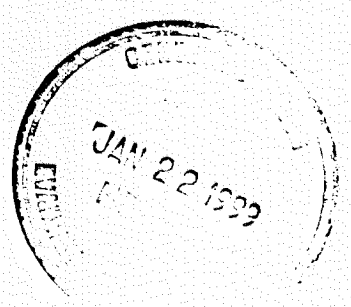
APPEARS THIS WAY ON ORIGINAL

Roche

Pharmaceuticals

January 21, 1999

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706



Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Rationale and Supporting Documentation for
Draft Labeling Previously Submitted 1/18/99

Reference is made to the sponsor's submission dated January 18, 1999 which was in response to the Agency's approvable letter dated May 12, 1998 for the above-named application. The purpose of this submission is to provide the rationale and supporting documentation for the draft labeling as mentioned in the submission of January 18, 1999.

Reference is also made to sponsor's previous submissions dated July 23, 1997, February 5, 1998 and April 9, 1998 which included draft labeling (professional and patient) for this application. Since it is our understanding that these previous labeling submissions were not reviewed by the Agency, the labeling included in the submission dated January 18, 1999 and in this submission supercedes those previous labeling submissions.

Reference is also made to the Agency's faxes dated March 27, 1997, April 28, 1997, April 29, 1997 and June 27, 1997 which included comments on the early versions of the sponsor's draft labeling. We have re-reviewed the Agency's input and the labeling in both the January 18, 1999 submission and in this submission includes the Agency's recommendations delineated in these faxes.

This submission includes professional and patient labeling and supporting documentation. All the Agency's previous requests with regard to labeling have been included and addressed in this draft labeling. The Agency's faxes addressed both general comments on the label as well as specific issues on specific text included in the previous versions of the draft label. The general comments on the label are addressed in the next paragraph of this letter and the specific issues on labeling text are addressed in the section of this submission identified as "Issues (1-25)".

In the fax dated June 27, 1997 the Agency had three general comments on the labeling which included that all tables should have titles, "tid" should be replaced by "three times a day" and p-values for pooled data should be deleted. Table titles have now been included throughout the label as requested. Although "tid"can be replaced with "three times a day", we have searched the electronic PDR and find that over 160 professional packages inserts use tid or t.i.d. compared to approximately 70 PIs using three times a day. We will comply with whichever designation the Agency requires but find that "tid" has been previously acceptable to the Agency for other products. Regarding the request to remove the p-value for

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

pooled data, we also note in the June 27 fax, the Agency requested us to designate which risk factors (based on pooled analysis) are not statistically significant. We note that pravastatin included the results of a pooled analysis and the p-value for that analysis is in their approved labeling. We also note that FOSAMAX includes the term "statistically significant" when referring to a pooled analysis in their approved labeling as well. It is our opinion that to discuss statistical significance or non-significance for a pooled analysis is misleading without the corresponding p-value. Please see the "Issues" section of this submission for a further discussion of the p-value for pooled analyses. For these reasons we have retained the p-values for pooled analyses in the draft label at this time.

Specific issues on labeling text are addressed in the section of this submission identified as "Issues (1-25)". The "Issues" section of the submission cites the Agency's issue, the sponsor's suggested text, the sponsor's rationale for the suggested text and, when necessary, it also references the supporting documentation. For ease of review the professional draft labeling has **[ISSUE No.]** imbedded in the text to indicate where the Agency had previously commented on specific text. The corresponding Issue No. in the "Issue" section of the submission contains a detailed discussion and suggested resolution of the issue for the Agency's further consideration.

Please feel free to contact the undersigned if you have any questions regarding this submission at the telephone and fax numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ:LS/km
Attachment
HLR No. 1999-151

PATENT INFORMATION[1]

1.	Active Ingredient(s):	Orlistat
2.	Strength(s):	120 mg
3.	Trade Name:	Xenical®
4.	Dosage form and Route of Administration	capsule, oral
5.	Application Firm Name:	Hoffmann-La Roche Inc.
6.	NDA Number:	20-766
7.	First Approval Date:	None[2]
8.	Exclusivity:	Subject to patent rights, first ANDA can be submitted five years from date of pending NDA approval.
9.	Patent Information:	
	Patent Number and Expiration date:	4,598,089 6/18/2004[3]
	Type of Patent:	Drug
	Patent Owner:	Hoffmann-La Roche Inc.

[1] While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

[2] Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

[3] Subject to patent term extension provisions for 35 USC § 156 et seq.

EXCLUSIVITY SUMMARY for NDA #20-766 SUPPL # _____

Trade Name Xenical Capsules Generic Name Orlistat

Applicant Name Hoffmann-La Roche HFD-510

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /N/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/ [redacted]

Signature

Title: Consumer Safety Officer

May 12, 1997

Date

/S/ [redacted]

Signature of Division Director

May 11, 1998

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20766	**Trade Name:**	XENICAL(ORLISTAT) 120
Supplement Number:		**Generic Name:**	ORLISTAT/TETRAHYDROLIPSTATIN
Supplement Type:		**Dosage Form:**	Capsule; Oral
Regulatory Action:	PN	**Proposed Indication:**	Xenical is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Xenical is also indicated to reduce the risk for weight regain after prior weight loss. Xenical is indicated for obese patients with an initial body mass index greater than or equal to 30 kg/m2 or greater than or equal to 27 kg/m2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN HESS

VSI [redacted]
Signature

4/9/99
Date

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-766 Trade (generic) names Xenical (orlistat) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

✓ ____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
✓ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: Initial discussion about conducting studies took place at the Advisory Committee meeting on MAY 14, 1997. The division will have further discussion with the sponsor at a later date.

/S/ [redacted]
Signature of Preparer

5/15/97
Date

cc: Orig NDA
HFD-510 /Div File
NDA Action Package

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 335a (a) and (b), in connection with this application.

April 19, 1999
Memorandum
To: the File NDA 20-766 Xenical Capsules (orlistat)
From: Solomon Sobel M.D.,Director Division of Metabolic and Endocrine Drug Products
Subject: Approval of NDA
This memo is a follow-up of my previous memo of May 11,1999 in which I found that orlistat was approvable if there were addditional data accrued supporting its safety in respect to breast cancer.
The sponsor has complied with our requests and has submitted the necessary data to provide reassurance in this regard.
See my concurrence of the medical review by Dr. Eric Colman of 3-22-99.
Recommendation: the Division recommends approval of the NDA at this time.
Solomon Sobel M.D.
/s/ [redacted] 4/19/99

cc:
NDA 20-766
HFD-510/Div. File
HFD-510/EColman/GTroendle/BStadel/MHess/MHaber/DWu/DHertig/RSteigerwalt/LPian/TSahlroot/